REMARKS

Claims 22-23, 26-30, and 35-45 are pending in this application. Claims 22-23 and 29-30 have been withdrawn from consideration. Claims 26, 28, 35-36, 38, 40 and 42 have been amended to expedite allowance and to place the application in better condition for appeal. Claims 37 and 41 have been canceled without prejudice. Accordingly, upon entry of this amendment, claims 22-23, 26-30, and 35-36, 38-40, and 42-45 will remain pending.

Claims 26, 35, 36, 38 and 40 have been amended to specify that the vaccine also comprises an immune stimulator. Support for this amendment can be found throughout the specification and claims, as originally filed, and/or in the claims as previously pending. For example, support can be found at page 7 (lines 1-12), page 18 (lines 1-4), page 46 (lines 6-15) and original claim 26.

No additional search should be required and no new issues have been raised by the amendments made herein. Furthermore, the number of issues for appeal have been reduced. Specifically, as discussed below, the Examiner's rejection under 35 U.S.C. §, first paragraph, has been obviated by the claim amendments (*i.e.*, to include an "immune stimulator") and cancellations. Moreover, since vaccine compositions comprising an "immune stimulator" have already been searched, the addition of this component should not require a further search.

In addition, Applicants respectfully note that the final rejection under 35 U.S.C. §, first paragraph, was raised for the first time in the most recent Office Action dated April 27, 2010 and was not necessitated by Applicants' previous amendments. Applicants believe that the rejection should not be final. Notwithstanding, Applicants are submitting the present Amendment in an earnest attempt to advance prosecution and to reduce the number of issues for appeal.

Request for Reconsideration of Finality of Office Action

Applicants respectfully traverse the finality of the rejections made in the present Office Action dated April 27, 2010. The finality of the present Office Action is improper because the Examiner has introduced a new ground of rejection not necessitated by Applicants' claim amendments as set forth in the Amendment and Response dated June 25, 2008 (MPEP 706.07(a)).

Specifically, the Examiner has finally rejected claims 26-27, 35-36, 39-40 and 43-45 as containing new matter (*i.e.*, the Examiner alleges that the specification does not teach a vaccine without an immune stimulator). However, this basis for this rejection could have previously been raised by the Examiner and it was not necessitated by Applicants' most recent claim amendments dated June 25, 2008. The claims as originally filed specified that the vaccine includes an immune stimulator (see original claim 26). In the Amendment and Response dated December 22, 2005, Applicants amended original claim 26 to remove the requirement that the vaccine include an "immune stimulator". Accordingly, the Examiner could have (but did not) raise a new matter rejection in the subsequent Office Action dated March 23, 2006 at that time. As such, raising the new matter rejection for the first time in the Final Office Action dated April 27, 2010 is improper. Applicants have been deprived of an opportunity to respond to the rejection prior to the final rejection of the present Office Action, and thus respectfully request that the finality of the present Office Action be withdrawn.

Rejection of Claims 26-28 and 35-45 Under 35 U.S.C. § 112, First Paragraph, as Failing to Comply with the Written Description Requirement

The Examiner has rejected claims 26-28 and 35-45 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that the specification does not provide adequate written description for the claimed invention because, while the specification discloses the full length sequence of murine DEC-205 protein, it only discloses a partial sequence for human DEC-205. The Examiner asserts that, because human DEC-205 is approximately 1800 amino acids in length, the recitation in the claim of a 30 or 25 amino acid sequence derived from human DEC-205 does not provide adequate written description of a molecule that is almost 1800 amino acids in length. The Examiner further asserts that the claims encompass antibodies that bind any immunogenic epitope on the approximately 1775 undisclosed amino acids of DEC-205, and that the term human DEC-205 presumably encompasses full length human DEC-205 , as well as undescribed mutants and alleles of human DEC-205. Additionally, with respect to claim 40, the Examiner is of the opinion that "in the absence of human DEC-205, it would not be possible to establish which antibodies reacted with human DEC-205."

Applicants respectfully traverse this rejection for the reasons previously made of record and as set forth below.

A. Each Independent Claim Requires Separate Consideration

Applicants respectfully disagree with the Examiner's rejection. As a preliminary matter, the scope of claims 26-28 and 35-45 varies and, as such, the assertions made by the Examiner are not equally applicable to all of these claims.

Specifically, contrary to the Examiner's opinion that the claimed antibody conjugates do not bind to any specific epitope of human DEC-205, claims 35-39 are drawn to antibody conjugates which do, indeed, bind to a particular epitope of human DEC-205, namely the C-terminal sequence (SEQ ID NO: 1).

Similarly, that the present specification teaches a partial human DEC-205 sequence is also irrelevant with respect to claims 40-45, since these claims are drawn to a vaccine comprising an antigen conjugated to an antibody that binds to *full length murine DEC-205 protein* (SEQ ID NO: 3). Thus, the Examiner's statement that the antibody conjugates of claims 40-45 bind to "undisclosed amino acids of DEC 205" is incorrect. Indeed, the full length sequence of murine DEC 205 is explicitly provided in the present application as SEQ ID NO: 3. Moreover, while the antibody conjugates of claims 40-45 also cross-react with human DEC-205, the epitopes of human DEC-205 that the conjugates bind to are thus, by definition, shared with (*i.e.*, cross-reactive with) murine DEC-205. As such, the sequence of these epitopes is provided as part of the full length murine DEC-205 sequence recited in the claims (SEQ ID NO: 3).

For at least the reasons above, the reasons provided by the Examiner for rejecting claims 35-45 as lacking written description under 35 U.S.C. §112, first paragraph, do not apply or support the rejection.

Finally, with respect to claims 26-28, drawn to a vaccine comprising an antigen conjugated to an antibody that binds to human DEC-205 protein comprising the partial amino acid sequence of SEQ ID NO: 1, Applicants respectfully submit that while Applicants' specification does not recite the full length human DEC-205 sequence, or the sequence of each and every variant of human DEC-205, this does not *de facto* mean that the pending claims fail to comply with the written description requirement. Importantly, it is well-established that the written description standard is not a bright line test, but instead takes into consideration a number of different factors. As discussed in detail below, Applicants' disclosure of the partial human DEC-205 sequence and the full length murine DEC-205 sequence, in combination with knowledge available in the art, were sufficient to demonstrate to one of ordinary skill that they

had full possession of the complete human DEC-205 protein, and antibody conjugates against the protein, at the time the present application was filed.

B. The Descriptive Text Needed to Satisfy the Written Description Standard Must be Considered in Relation to the Scientific Knowledge in Existence at the time of the Invention, the Skill in the Art, and Correlation of a Disclosed Function to a Known Structure

The mere fact that Applicants' specification does not recite the full length human DEC-205 sequence does not alone mean that any of the claims on appeal fail to comply with the written description requirement.

Moreover, Applicants respectfully disagree with the Examiner's assertion that the decision in *Capon v. Eshhar* (418 F.3d 1349, 1357 (Fed. Cir. 2005)) "is not relevant to the claims under consideration." While the claims on appeal may differ from the claims on appeal in *Capon v. Eshhar*, the Court took considerable effort to lay out the underlying framework for determining written description in other cases moving forward, and to clarify that written description, like enablement, must be determined on a case by case basis. Specifically, the standard for meeting the written description requirement and showing possession of the claimed invention, as articulated by *Capon v. Eshhar*, differs for every patent specification depending upon a number of factors, including the scientific knowledge in existence at the time of the invention, the skill in the art, the predictability of the claimed subject matter, and correlation of a described function to a known structure. Again, Applicants do not argue that the claims at issue in *Capon v. Eshhar* were the same as in the present case, rather that the written description standard articulated by the Court, when applied in the present case, is fully satisfied.

Specifically, as discussed further below, the maturity of the science and skill in the art at the filing date of the present invention were such that one of ordinary skill could predictably obtain full-length proteins, such as DEC-205, based on partial sequences, as well as predictably obtain antibodies against the full-length protein (or any region or variants of the protein). As such, Applicants teachings in the specification, combined with the knowledge available in the art, demonstrate that Applicants were in full possession of the presently claimed invention at the time of filing.

C. Isolation and Cloning of Proteins, and Generation of Antibodies Were Highly Mature Technologies at the Time of the Present Invention

At the filing date of the present application (*i.e.*, in 1995), technologies for isolating, characterizing and cloning proteins were highly developed, as were technologies for generating antibodies against such proteins. For example, several well known techniques were available for cloning proteins, including human DEC-205, based on a given partial amino acid sequence of the protein (see, for example, page 20, line 30 through page 21, lines 1-19; as well as page 25, lines 25-31 through page 31, lines 1-16 of the present application). Additionally, techniques for expressing cloned proteins (see, for example, page 31, lines 18-31 through page 35, lines 1-30 of the present application) and for generating antibodies against the proteins were equally well known (see, for example, page 42, lines 23-31 through page 45, lines 1-19, and particularly page 42, lines 28-31 in the present application). Once armed with a partial amino acid (*i.e.,* a peptide derived from a given protein), it was also well within the skill of the art to use these techniques to generate antibodies against such peptides and to isolate the full-length protein from its natural source.

Applicants specifically illustrated this in relation to mouse DEC-205. In particular, Applicants successfully isolated and characterize full-length mouse DEC-205 from whole murine thymus using mAb NLDC-145, an anti-mouse DEC-205 antibody (see page 63 of the present application). Additionally, Applicants successfully raised antibodies against N-terminal peptides from mouse DEC-205 protein (see, for example, page 62, lines 26-32 and page 63, lines 1-15 of the present application). This provides evidence that using a partial sequence puts one in possession of a full length sequence, and, thus, could have been applied using the partial human sequence in the present application.

Additionally, in the present application, Applicants teach a partial (C-terminal) sequence (SEQ ID NO: 1) of human DEC-205 protein. Applicants further teach the highly homologous full-length sequence of mouse DEC-205 protein (SEQ ID NO: 3), along with an in-depth characterization of this protein (including its ability to deliver antigen to an active antigen processing compartment of dendritic cells). Applicants also describe well-known techniques for cloning proteins (including human DEC-205) based on a given partial amino acid sequence of the protein, expressing cloned proteins and generating antibodies against the proteins. Based on these teachings, it would have been well within the skill of the art to have isolated the full-length

human DEC-205 protein, as well as variants of the human DEC-205 protein, and generate antibodies against this protein.

In fact, as evidenced by the Declaration by Dr. Michel Nussenzweig (Appendix A), the cloning techniques and techniques for generating antibodies described in the specification were ultimately successfully used to clone and isolate human DEC-205 and to produce antibodies against full-length human DEC-205. This provides clear evidence that Applicants were in fact indeed in possession of the claimed invention based on the descriptive text provided within the four corners of Applicants' originally filed disclosure.

Rejection of Claims 26-28 and 35-39 Under 35 U.S.C. § 112, First Paragraph, as Failing to Comply with the Written Description Requirement

The Examiner has rejected claims 26-28 and 35-39 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner alleges that there is no support in the specification for a "human DEC-205 protein comprising an amino acid sequence as set forth in SEQ ID NO: 1 in claim 26/35." The Examiner further asserts that, "none of the passages disclose human DEC-205 protein comprising an amino acid sequence as set forth in SEQ ID 7 in claims 6/13." Specifically, the Examiner is of the opinion that

> [w]hilst the specification discloses SEQ ID NO 7 as a peptide derived from DEC-205, there is no disclosure in the specification as originally filed of a DEC-205 protein comprising said peptide wherein the molecule could have any other amino acids in association with the aforementioned sequences recited in the claim.

Applicants respectfully traverse this rejection for the reasons previously made of record and as set forth below.

As an initial point, it is unclear to Applicants, based on the Examiner's comments, what the distinction is between the former 35 U.S.C. § 112, first paragraph, rejection of claims 26-28 and 35-45, and the present § 112, first paragraph, rejection of claims 26-28 and 35-39. Indeed, both rejections appear to be based on the same premise, *i.e*, that the claims lack written description because the specification teaches a partial human DEC 205 sequence. Applicants note, however, that the former rejection has been applied to claims 26-28 and 35-45, whereas the present rejection has been applied only to claims 26-28 and 35-39.

Accordingly, with respect to claims 35-39, Applicants again respectfully note that these claims are drawn to a vaccine that employs antibody conjugates defined as binding to a *particular* epitope on human DEC 205, the sequence of which is explicitly taught in the application (SEQ ID NO: 1, not SEQ ID NO: 7, as noted by the Examiner). Therefore, the Examiner's assertion that the specification fails to provide support for a human DEC 205 protein comprising the partial sequence of SEQ ID
NO: 1 does not provide a basis for rejecting claims 35-39 for lack of written description.

Moreover, for the many reasons discussed above in Section B, Applicants respectfully submit that the specification does indeed provide full support for a human DEC 205 protein comprising SEQ ID NO: 1, as recited in claims 26-28. Again, the mere fact that the disclosure teaches partial sequences for human DEC 205 does not alone mean that the claims covering antibody conjugates which bind to human DEC 205 comprising such sequences lack written description. Whether claims 26-28 comply with § 112, first paragraph, depends on a variety of factors, as discussed above in relation to the previous rejection (Section B). When applied in the present case, given the teachings in Applicants' specification, in combination with the skill and knowledge available in the art at the time the present application was filed, clearly demonstrate that Applicants possessed the complete human DEC-205 protein recited in claims 26-28.

As previously discussed in detail, Applicants teach the partial C-terminal sequence of human DEC-205 (SEQ ID NO: 1). Based on this partial amino acid sequence, it was well within the skill of the art to have used known techniques to generate antibodies against this peptide, and to have predictably isolated the full-length protein or variants from its natural source. In fact, the maturity of the science and skill in the art at the time of the present invention were such that those of ordinary skill in the art were routinely obtaining full-length proteins based on partial sequences, as well as predictably obtaining antibodies against such full-length proteins. This is specifically attested to in the Declaration submitted by Declaration by Dr. Michel Nussenzweig (Appendix A). Further, the fact that Applicants provide an in-depth characterization of mouse DEC-205, including its full-length sequence, which correlates to human DEC-205, provides further basis for fully meeting the Written Description requirement.

In sum, for at least the foregoing reasons, claims 26-28 and 35-39 fully comply with 35 U.S.C. § 112, first paragraph.

Rejection of Claims 26-27, 35-36, 39-40, and 43-45 Under 35 U.S.C. § 112, First Paragraph, as Failing to Comply with the Written Description Requirement

The Examiner has rejected claims 26-27, 35-36, 39-40, and 43-45 under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. Specifically, the Examiner is of the opinion that the specification and claims as originally filed do not disclose a vaccine without an immune stimulator.

Applicants respectfully traverse this rejection. Notwithstanding, to expedite prosecution and allowance of the pending claims, Applicants have amended claims 25, 35-36, and 40 to specify an "immune stimulator," thereby obviating this rejection. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 26-28 and 35-45 Under 35 U.S.C. § 112, First Paragraph, as Failing to Comply with the Enablement Requirement

The Examiner has rejected claims 26-28 and 35-45 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner is of the opinion that the specification fails to disclose how to use the presently claimed methods for the in vivo treatment of disease in humans. The Examiner further asserts that "there is no disclosure in the specification of any in vivo evidence in any model wherein the claimed invention is used as a vaccine or tumor vaccine."

Applicants respectfully traverse this rejection for the reasons previously made of record and as set forth below.

A. Enablement of Composition of Matter

MPEP 2164.02 provides that "***any enabled use*** that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use" (emphasis added). Accordingly, as applied to the present case, the claimed vaccines are clearly enabled. Specifically, in addition to *in vivo* gene therapy, the claimed vaccines are also at least enabled for ***in vitro*** uses, such as, testing, evaluating, and/or comparing the function, *e.g.*, antigen presentation, of DEC-205 receptors. In this regard, it is important to note that the

present claims are drawn to vaccines (*i.e.*, compositions of matter), not to specific *in vivo* uses, although Applicants maintain that such *in vivo* uses are fully enabled.

Indeed, as discussed below, working examples are not required to enable an invention. Rather, the disclosure of working examples supporting a claimed invention is only one factor to be considered in determining whether the invention is enabled, and is not solely determinative of the issue.

B. In Vivo Data or Working Examples Are Not a Necessary Requirement for Enablement

In response to the Examiner's suggestion that working examples are required to satisfy the enablement standard, Applicants respectfully note that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether *in vivo* data or working examples are disclosed (M.P.E.P. § 2164.02). This is particularly true for a composition of matter claim, such as the claims in the present application. In fact, the specification need not contain *in vivo* data or working examples if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)) and, importantly, ***if one of ordinary skill in the art would reasonably accept the supporting disclosure as being enabling based on the teachings and/or data that is provided*** (*In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)). In the present case, this standard is satisfied, notwithstanding the fact that the claims are clearly enabled for *in vitro* uses as well.

Contrary to the Examiner's assertion that the present specification fails to provide "appropriate evidence as to how the instant invention could be used for the in vivo treatment or prevention of disease in humans," the specification does indeed provide sufficient teachings, when combined with the knowledge in the art at the time the present application was filed, for one of ordinary skill to have practiced the claimed methods without undue experimentation.

For example, Applicants note the multiple examples provided in the present specification which unequivocally demonstrate that DEC-205 receptors are internalized after being bound by anti-DEC-205 antibodies (see, *e.g.*, pages 69-70). Applicants further exemplify the successful presentation of rabbit IgG-peptide/MHC complexes to T cell clones using rabbit-anti-DEC-205 antibodies (see, *e.g.*, pages 69-71). Such data, combined with the level of skill in the art, at the

time the present application was filed (as exemplified in co-pending application number 09/925,284, published as US 20020187131), provide evidence that the claimed vaccines are fully enabled.

For example, further evidence that the claims are fully enabled for *in vivo* vaccine therapy is provided by the *in vivo* working examples (conducted in mouse models) described in co-pending application number 09/925,284 (US 20020187131). Indeed, as provided in M.P.E.P. § 2164.02, "[a]n *in vitro* or *in vivo* animal model example ..., in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention...***if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate***. As discussed below, mice were routinely used and accepted animal models at the time of filing. Accordingly, the Examiner must accept the present specification as enabling, unless there is evidence to the contrary.

Specifically, as described in USSN 09/925,284 *in vivo* experiments in mice were successfully performed which demonstrated that (1) antigen delivered to dendritic cells *in vivo* induces persistent T cell activation (see page 37, line 14 through page 38, line 7, of application number 09/925,284), (2) the absence of persistent T cell activation in mice injected with an anti-DEC-205 antibody fused to hen egg lysozyme (αDEC/HEL) is not due to a lack of antigen and, therefore, that targeting of antigen to DEC-205 causes persistent T cell activation (see page 38, lines 7-16, of application number 09/925,284), and (3) techniques for assessing dendritic cell function in mice receiving multiple doses of an anti-DEC-205 antibody fused to hen egg lysozyme (αDEC/HEL) (see page 38, line 18 through page 39, line 3, of application number 09/925,284). In view of these *in vivo* working examples and the fact that mice were (and still are) widely accepted animal models for assessing the clinical value of biological therapeutics, one of ordinary skill in the art would not reasonably doubt that the disclosed mouse data correlates with the claimed invention, nor that the presently claimed methods are fully enabled.

In addition, as discussed below, mouse models have long been accepted in the field as being reasonably correlative of human treatment. While clinical studies in humans may ultimately be required to establish human treatments and therapeutic regimens, ***it is readily acknowledged in the art that the basic molecular principle behind a particular method of treatment is often first identified in a murine model***. As exemplified in USSN 09/925,284, the present specification fully enables the development of in vivo immune tolerance by targeting an

antigen to dendritic cells using anti-DEC-205 antibodies. The discovery of this molecular principle of tolerance was a typical and pivotal first step in establishing a pervasive concept for disease treatment.

C. Level of Predictability in the Art

The Examiner further asserts that *in vivo* treatment using the presently vaccine conjugates is unpredictable in view of the teachings provided in the prior art. Applicants respectfully traverse this rejection.

From the outset, Applicants again note that the present claims are drawn to vaccines (*i.e.*, compositions of matter), not to specific *in vivo* uses. Therefore, the standard of enablement is met by showing at least one enabled use, which Applicants do. As exemplified in the present application, and described in detail above, multiple examples are provided in the present specification which predictably show the use of the claimed vaccines for testing, evaluating, and/or comparing the function, *e.g.*, antigen presentation, of DEC-205 receptors. Therefore, the predictability of *in vitro* uses of the claimed vaccines is high. Further, as described further below, *in vivo* treatment using the claimed vaccines is also predictable.

In particular, Applicants' disagree with the Examiner's statements regarding the cited reference, Schjetne *et al.* (*J. Immunol.* 2007 Apr 1;178(7):4169-76). Specifically, the Examiner maintains that it is "unpredictable whether human disease can be treated via enhancing tolerance to a disease antigen" in view of Schjetne *et al.* The Examiner relies on Schjetne *et al.* as teaching that "DEC205 antigen conjugates administered in vivo require CD40 ligation in vivo in order to induce an immune response (see page 4169, second column, first paragraph)" and concludes that "the claimed invention would not be expected to induce an immune response" or to treat disease in humans "because it lacks an agent that causes CD40 ligation." Further, with respect to the use of the invention as a tumor vaccine, the Examiner asserts that Schjetne *et al.* "teach that even in the presence of CD40 ligation...tumor vaccines would be unsuitable for treating tumor bearing animals (see page 1475, first page, last paragraph)."

Contrary to the Examiner's suggestion, Schjetne *et al.* do not support a lack of predictability for the presently claimed vaccines which include targeting an antigen to the DEC-205 receptor, an efficient endocytic receptor. Indeed, as explained by Schjetne *et al.*, their results only apply when the antigen is inefficiently endocytosed by antigen presenting cells, *e.g.*,

when the antigen is **not targeted to the DEC-205 receptor**, as currently claimed. Specifically, Schjetne *et al.* state:

> ... the requirement for a physical linkage between the Ag and the maturation signal in the present experiments superficially appears to contradict recent in vivo studies demonstrating induction of long-lasting T cell responses even when anti-CD40 mAb was not linked to the Ab-Ag fusion protein ... The difference might be explained by the fact that in the latter case, the recombinant Ab-Ag fusion was targeted to DEC205, an efficient endocytic receptor expressed on DC ..., but lacking the ability to induce a maturation signal.. Thus, **linkage between the CD40-targeting unit and the Ag might only be required if the Ag is otherwise inefficiently endocytosed by APC, as was the case in the design of the present study** (emphasis added).

Moreover, with respect to the value of using animal models as a preliminary step in establishing a concept for disease treatment in humans, Applicants refer to the enclosed publications by (1) Tufveson *et al.* (Immunol Rev. 1993 Dec;136:99-109), and (2) Mestas *et al.* (*J Immunol.* 2004 Mar 1;172(5):2731-8).

Specifically, while Tufveson *et al.* (Immunol Rev. 1993 Dec;136:99-109) suggest that data from small animal models should not be the *sole basis* for "clinical decision making"... the authors also state that "it is evident that animal experiments to support modes of clinical action are warranted" (see page 101). Similarly, while Mestas *et al.* point out that mice and humans have obvious differences that "should be taken into account when using mice as preclinical models of human disease," the authors teach that "***[m]ice are the experimental tool of choice for the majority of immunologists and the study of their immune responses has yielded tremendous insight into the workings of the human immune system***" and that "***mice are the mainstay of in vivo immunological experimentation and in many respects they mirror human biology remarkably well***" (see page 2731).

Moreover, contrary to the Examiner's suggestion that *in vivo* treatment using the presently claimed methods is unpredictable in view of teachings available in the art, Applicants respectfully note that there is ***substantial evidence*** in the art to demonstrate that a molecular principle ***can*** be predictably applied to the development of human therapeutics, once a principle has been identified and tested, for example, in an animal disease model (*e.g.*, an *in vivo* murine disease model). For example, Tysabri, an anti-VLA4 treatment for multiple sclerosis in humans, was presaged by Lawrence Steinman's anti-VLA studies of experimental allergic encephalomyelitis (EAE) in mice; see, for example, Yednock *et al.* (1992) *Nature* 356: 63-66,

which concluded that "... therapies designed to interfere with alpha 4 beta 1 integrin may be useful in treating inflammatory diseases of the central nervous system, such as multiple sclerosis." Similarly, Copaxone treatment for multiple sclerosis in humans, was presaged by Ruth Arnon's and Michael Sela's studies with copolymers in EAE in mice and the discovery of synthetic peptides as model antigens; see, for example, Teitelbaum D. *et al.* (1971) *Eur. J. Immunol.* 1: 242-248 which concluded that "[i]n its suppressive activity (the copolymer), it is as effective as the brain encephalitogen itself and thus may be of help both in studies of the mechanism of EASE and as a potential suppressive agent for EAE and other diseases of a similar nature." Additionally, FDA approved IL-2 treatment of cancer in humans was presaged by Steve Rosenberg's studies of mouse melanoma rejection in mice; see, for example, Rosenberg *et al.* (1985) *J. Exp. Med.* 161: 1169-1188, which concluded that "[t]he ready availability of high doses of recombinant human IL-2, and the demonstration of antitumor effects seen in animal models have led us to the initiation of the clinical trials of recombinant IL-2 in humans." Finally, CTLA-4 blockade, for which FDA approval is currently being sought as a new weapon in the treatment of cancer in humans, was presaged by Jim Allison's studies of anti-CTLA treatment of mouse tumors and the discovery of CTLA-4 as a counter-receptor for costimulatory B7 molecules in mice; see, for example, Leach *et al.* (1996) *Science* 271: 1734-1736, which concluded that "[t]hese results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effect immune responses against tumor cells."

These are but a few examples evidencing that a molecular principle ***can*** be predictably applied to the development of human therapeutics. Accordingly, it is clear that *in vivo* mouse models of experimentation are widely accepted as playing a key, initial role in the establishment of methods and therapeutics for treating human disease. As such, it is clear that the working examples set forth in Applicants' specification provide more than sufficient evidence to enable the ordinarily skilled artisan to make and use the claimed invention using only routine experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the foregoing remarks, reconsideration and withdrawal of all rejections and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

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